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EXAMINER	
TON, THAIAN N	

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1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/810,311	MANDALAM ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-22 are pending; claims 19-20 are withdrawn; claims 1-18, 21 and 22 are under current examination.

Election/Restrictions

Claims 19-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 5/1/07.

Additionally, Applicants elected HNF4b, Albumin, ApoCII, DMSO, BMP and HGF and BMP for the species requirement, in the Response filed 10/5/07.

Applicant's election without traverse of Group I, claims 1-18,21 and 22 in the reply filed on 5/1/07 is acknowledged.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting

application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 5-8, 11, 12, 21, 22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Pat. No. 7,256,042.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to methods of differentiating pPS cells into differentiated cells that have the morphological features of hepatocytes. The instant claims are directed to methods for differentiating primate pluripotent stem (pPS) cells into hepatocyte lineage cells in at least three discrete steps comprising: a) culturing the undifferentiated pPS cells with a means for causing differentiation of the cells into cells having the characteristics of fetal endoderm; b) culturing the cells from step a) with a means for causing differentiation of fetal endoderm cells into cells have characteristics of hepatocyte progenitor cells; c) culturing the cells from b) with a means for causing the differentiation of hepatocyte progenitor cells into cell shaving characteristics of mature hepatocytes. Further embodiments limit the markers which the cells express, as well as the culture conditions to produce the cells of steps a), b) and c). The '042 claims are directed to producing hepatocyte lineage cells, wherein the claims are directed to the same factors as the instant claims, such as sodium butyrate, DMSO, and various growth factors (see claim 6).

Accordingly, given that both sets of claims are direct to producing hepatocyte cells from primate pluripotent cells, and both sets of claims recite

the same factors to produce the hepatocyte cells, the instant claims are rendered obvious by the '042 claims.

Claims 1, 5-8, 11, 12, 21, 22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Pat. No. 7282366.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to methods of differentiating pPS cells into differentiated cells that have the morphological features of hepatocytes. The instant claims are directed to methods for differentiating primate pluripotent stem (pPS) cells into hepatocyte lineage cells in at least three discrete steps comprising: a) culturing the undifferentiated pPS cells with a means for causing differentiation of the cells into cells having the characteristics of fetal endoderm; b) culturing the cells from step a) with a means for causing differentiation of fetal endoderm cells into cells have characteristics of hepatocyte progenitor cells; c) culturing the cells from b) with a means for causing the differentiation of hepatocyte progenitor cells into cell shaving characteristics of mature hepatocytes. Further embodiments limit the markers which the cells express, as well as the culture conditions to produce the cells of steps a), b) and c).

The '366 claims are directed to methods for producing hepatocytes lineage cells by culturing the pPS cells in a growth environment that comprises one or more hepatocytes maturation factors that are either an organic solvent selected from DMSO, DMA, hexamethylene biascetamide, and other polymethylene bisacetamides; or b) a cytokine or hormone selected from glucocorticoids, EGF, insulin, TGF-α, TGF-β, FGF, HGF, IL-1, IL-6, IGF-II and HBGF-1. The '042 claims are directed to producing differentiated cells from primate pluripotent stem cells by culturing the pPS cells in

butyrate, and in specific embodiments, the differentiation is initiated by culturing the cells in DMSO, DMA, hexamethylene biascetamide, and other polymethylene bisacetamides and further, culturing the cells in a medium containing a cytokine or hormone.

Accordingly, given that both sets of claims are direct to producing hepatocyte cells from primate pluripotent cells, and both sets of claims recite the same factors to produce the hepatocyte cells, the instant claims are rendered obvious by the '366 claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18, 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

1. Methods of differentiating human ES cells (hES) into mature hepatocytes comprising:

i) culturing ES cells to form embryoid bodies;

ii) culturing the embryoid bodies in medium containing 20% FBS and 5 mM sodium butyrate to produce mature hepatocytes.

2. Methods of differentiating hES cells into mature hepatocytes comprising:

i) culturing undifferentiated hES cells in a feeder-free condition, comprising an extracellular matrix and fibroblast conditioned medium;

ii) culturing hES cells of (i) with 1% DMSO;

iii) culturing the cells of (ii) with sodium butyrate to produce hepatocytes

iv) culturing the cells of (iii) with hEGF, TGF-α, HGF, DMSO and butyrate to produce mature hepatocytes.

3. Methods of differentiating hES cells into mature hepatocytes comprising:

i) culturing hES cells with fibroblast-conditioned medium and 8 ng/ml of bFGF;

ii) culturing the cells of (i) with serum replacement and DMSO;

iii) culturing the cells of (ii) with EGF and HGF

iv) culturing the cells of (iii) with dexamethazone, HGF and EGF to produce mature hepatocytes.

4. Methods of differentiating hES cells into mature hepatocytes comprising:

i) culturing hES cells with fibroblast-conditioned medium and 8 ng/ml of bFGF;

ii) culturing the cells of (i) with serum replacement and DMSO;

iii) culturing the cells of (iii) with DMSO, HGF and dexamethazone;

iv) culturing the cells of (iv) with EGF, HGF, dexamethasone and DMSO to produce mature hepatocytes.

5. Methods of differentiating hES cells into mature hepatocytes comprising:

i) culturing hES cells in fibroblast-conditioned medium containing 8 ng/ml of bFGF; and

ii) culturing the cells of (i) with FGF-8; and

iii) culturing the cells of (ii) on gelatin coated plates or a feeder layer, in the presence of 10 ng/ml of bFGF; and

iv) culturing the cells of (iii) in the presence of BMP-2, BMP-4, BMP-6 and dexamethazone; and

v) culturing the cells of (iv) in the presence of BMP-2, BMP-4, BMP-6 and oncostatin M; and

vi) culturing the cells of v) in the presence BMP-2, BMP-4, BMP-6 and oncostatin M, dexamethazone and NGF;

v) culturing the cells of vi) in the presence of dexamethasone, NGF and HGF, thereby producing mature hepatocyte cells.

The specification does not reasonably provide enablement for the breadth of the claims, which encompass any means for differentiation hES cells , or the breadth of any combination of growth factors, to produce mature

hepatocytes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention. The claimed invention is directed to methods for differentiating primate pluripotent stem (pPS) cells into hepatocyte lineage cells in at least three discrete steps comprising: a) culturing the undifferentiated pPS cells with a means for causing differentiation of the cells into cells having the characteristics of fetal endoderm; b) culturing the cells from step a) with a means for causing differentiation of fetal endoderm cells into cells have characteristics of hepatocyte progenitor cells; c) culturing the cells from b) with a means for causing the differentiation of hepatocyte progenitor cells into cell shaving characteristics of mature hepatocytes. Further embodiments limit the markers which the cells express, as well as the culture conditions to produce the cells of steps a), b) and c).

Breadth of the claims. The claims broadly encompass using any means for producing cells having characteristics of fetal endoderm from pPS cells; any means for causing differentiation of the endoderm cells into hepatocyte progenitor cells; using any means for causing differentiation of hepatocyte progenitor cells into cells with characteristics of mature hepatocytes.

Guidance of the Specification/The Existence of Working Examples. The specification teaches the differentiation of human ES cells to embryoid bodies and then culturing the embryoid bodies in medium containing 5 mM sodium butyrate to produce primary hepatocytes (Example 1). The specification

teaches the analysis of these cells showed that the differentiated cells were mature hepatocytes (Example 2, lines 17-18). The specification teaches that various analogs of butyrate were tested at 5 mM (propionic acid, isovaleric acid and isobutryate), which were effective in producing hepatocytes. Trichostatin A was found to induce hepatocyte differentiation at 75-100 nM. See page 29. The specification teaches the formation of hepatocytes without the formation of embryoid bodies by maintaining human ES cells in an undifferentiated state using medium conditioned by mouse embryonic fibroblasts and then culturing the cells with unconditioned SR medium containing 1% DMSO. The medium was then changed after 4 days to unconditioned SR medium containing 2.5% sodium butyrate to produce hepatocytes. See Example 3. The specification further teaches culturing human ES cells in mEF conditioned medium with added bFGF, and then changing the medium to HCM containing 10 ng/mL EGF plus 2.5 ng/mL HGF to produce hepatocyte lineage cells. See Example 5. The specification teaches producing hepatocyte lineage cells by culturing human ES cells in mEF conditioned medium, containing 8 ng/ml of BFGF, after 5 days, the cells were the cultured in KO-DMEM containing 1% DMSO. The cells were then cultured in HCM with 2.5 ng/ml HGF plus 0.1 μM dexamethazone and 1% DMSO, and then cells were then matured in a medium containing 10 ng/ml HGF, and plus 0.1 μM dexamethazone with/without 10 ng/ml of oncostatin M. The resultant cells had hepatocyte morphology. See Example 6. The specification teaches a method of producing hepatocytes using various growth factor protocol which produced cells with the same morphology, gene expression and enzyme analysis.

State of the Art/Predictability of the Art. The state of the art of directly differentiating an ES cell into a cell type of interest is not predictable. For example, Verfaillie *et al.* [Hematology (Am Soc Hematol Educ Program). 2002;:369-91] who review the state of the art of stem cells at the time of

filing, teach, that, with regard to the directed differentiation of ES cells, "Many proposed applications of human ES cells are predicated on the assumption that it will be possible to obtain pure populations of differentiated cells from the ES cultures. It might be envisioned that in order to achieve this one would treat ES cells with inducing agents that would convert them with high efficiency to a cell type of interest. In practice, that has not proven possible with the mouse system." See p. 278, 2nd column, Differentiation in vitro. Verfaillie teach that the ES cells can be treated with particular agents/factors that can drive differentiation along a specific lineage (see p. 379, 1st column, 1st full ¶. However, it is clear that directed differentiation of ES cells to generate a particular cell type of interest is unpredictable. Thus, specific guidance must be provided to enable the claimed invention. In the instant case, the specification teaches that specific factors and conditions have been found to produce hepatocyte cells. However, the breadth of the claims encompass any means to cause differentiation of primate pluripotent stem cells to produce hepatocytes (see claim 1, for example). Additional claims are directed to various combinations of growth factors or factors that would be used in order to produce hepatocytes. However, the breadth of these claims is not enabling. For example, claim 13 recites culturing cells with "one or more growth factors" in combination with Oncostatin M. However, the specification only teaches specific growth factors, in specific combinations would result in producing hepatocytes (see enabled scope).

Additionally, the post-filing art shows that producing hepatocytes is not predictable. For example, Lavon *et al.* (J. of Cell. Biochem., 96: 1193-1202, 2005) is post filing art that teaches that, "Although many protocols for differentiating ES cells to hepatic cells have been developed, the analysis of their status is not trivial and can lead to various conclusions." See Abstract. They note that differentiation of ES cells in culture is heterogeneous,

therefore to study directed differentiation, there is a need to define markers that are cell-specific." Additionally, they note that because the process of differentiation is gradual, there is a need to discriminate between genes expressed in each phase of development. See p. 1196, 2nd col., 2nd ¶. They additionally caution that, "As we described above, there are various ways to cause ES cells to differentiate into hepatic-like cells. However, the nature of the hepatic-like cells should be analyzed very carefully under several constrictions. (a) most of the genes that are expressed in the liver tissue are also expressed in the extra embryonic yolk sac tissue. AFT, TTR and FOXA2 for example, are widely expressed in both tissues and were widely used to characterize the differentiated cells as hepatocyte. In order to discriminate between these two populations of cells, we should identify discrete markers for hepatocytes and yolk sac tissues." See pp. 1999-1200, bridging ¶.

Similarly, Cai *et al.* (**Hepatology**, 45: 1229-1239, 2007) is post-filing art that states that, "Several studies have demonstrated the capacity of hESCs to differentiate into hepatocytes or hepatocyte-like cells. However, their differentiation efficiency is low and most reports performed only limited phenotypic and functional tests on the differentiated cells. In particular, the differentiation strategies previously employed do not exclude the extraembryonic endoderm differentiation of ESCs, which makes the hepatic identities of differentiated cells controversial. This is especially important for hESC differentiation, as hESCs tend to differentiate toward extraembryonic endoderm cells, which also express most of the hepatocyte markers. See pages 1229-1230, bridging ¶.

The Amount of Experimentation Necessary. The claims are not enabled for their breadth, because the state of the art of directed differentiation of ES cells to a particular cell type, is not found to be predictable, and the working examples in the specification fail to support that culturing pPS cells with "a means" as broadly claimed, would result in

hepatocyte lineage cells. In the instant case, the working examples provide specific growth factors and conditions in which to arrive at claimed invention. Given that the state of the art supports that it would be unpredictable to use any means to produce hepatocytes, and further, that various methodologies failed to distinguish hepatocytes from extraembryonic endoderm cells, it would have required undue experimentation for one of skill in the art to determine the specific combination(s) of growth factors or conditions, other than what has been described in the enabled scope above, in order to practice the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-18, 21, 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is unclear. The preamble of the claim relates to producing "hepatocyte lineage cells" but the method steps in the claims produce "mature hepatocytes". Therefore, the method steps do not relate back to the preamble. The term "hepatocyte lineage cells" in the preamble is broader than the "mature hepatocytes" that are produced. Appropriate correction is required. Claims 2-10, 21 and 22 depend from claim 1.

The term "most of" in claims 2-4 is a relative term which renders the claim indefinite. The term "most of" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Particularly, it is unclear what the metes and bound of the term "most of" encompass, therefore the claims are indefinite.

Claims 5-7 are confusing and unclear. The claims recite culturing the cells with various factors, but it unclear what is included or excluded in these claims. For example, claim 5 recites culturing the cells with DMSO, FGF-8, or a BMP, it is unclear if only the BMP is optional and DMSO and FGF-8 are required, or all factors are recited in the alternative. Claims 6-7 are similarly unclear.

Claims 8-10 are unclear. The claims recite, "culturing the cells" in line 1 of the claims. It is unclear which cells these refer to, as claim 1 refers to at least three different types of cells 1) the starting material, undifferentiated pPS cells, the fetal endoderm cells produced in step a), the hepatocyte progenitor cells produced in step b) and the mature hepatocytes produced in step c).

Claims 11, 13, and 16 are incomplete. Each of the claims recites a process for differentiating hES cells into hepatocyte lineage cells, but the method steps do not relate back to producing hepatocyte lineage cells. Claim 12 depends from claim 11; claims 14-15 depend from claim 13; claims 17 and 18 depend from claim 16. Appropriate correction is required.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Peter Paras, SPE of Art Unit 1632, at (571) 272-4517. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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